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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,814	07/26/2001	Madeline M. Butler	ISPH-0587	6393

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

SM.

Advisory Action	Application No.	Applicant(s)	
	09/915,814	BUTLER ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 May 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1.☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2.☒ The proposed amendment(s) will not be entered because:

(a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

(b) ☐ they raise the issue of new matter (see Note below);

(c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3.☐ Applicant's reply has overcome the following rejection(s): _____.

4.☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5.☐ The a)☐ affidavit, b)☐ exhibit, or c)☐ request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.

6.☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7.☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: *none*.

Claim(s) objected to: _____.

Claim(s) rejected: *1,2,4-15,72-83*.

Claim(s) withdrawn from consideration: _____.

8.☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9.☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10.☐ Other: _____

Attachment

The amendments filed 5-24-04 will not be entered because they introduce new limitations that would require further searching (i.e. the amendments introduce regional limitations of SEQ ID NO: 3 which are specifically targeted by antisense). The arguments addressing the failure of the art of record to target the specific regions of hsl that now appear in the proposed amendments are therefore not addressed below.

Applicants' arguments addressing the anticipatory references of Langin and Holst filed 5-24-04 have been fully considered but they are not persuasive. Applicants argue that Langin and Holst disclose antisense oligonucleotides between 8 and 50 nucleobases, but fail to disclose hybridization conditions or specific sequences and so cannot be expected to inhibit hsl expression to any degree in any cell type. Applicants also suggest that extreme conditions can be used to force almost any two single stranded nucleic acids to hybridize regardless of sequence complimentarity and therefore no assumption can be made about the antisense oligonucleotides disclosed by Langin and Holst regarding their ability to specifically target and inhibit hsl expression to any degree in HepG2 cells in vitro. Contrary to Applicants' assertions, Holst teaches an antisense oligonucleotide that specifically hybridized to the target hsl nucleic acid under "standard conditions" (see 4th full paragraph on page 442 of Holst). Langin teach a 21 nucleobase antisense oligonucleotide that hybridized to the target hsl nucleic acid at 42°C , and under conditions conducive for enzymatic reverse transcription. (see last paragraph on the left on page 4898 of Langin.) These conditions utilized by either

Langin or Holst are not extreme conditions as suggested by Applicant, but instead are conditions under which an oligonucleotide which is complementary to a target nucleic acid would be reasonably expected to specifically hybridize and inhibit transcription.

Applicants argue that the worker of ordinary skill would have no reason to consider the disclosures of either Holst or Langin in an obviousness rejection because these references relate to cloning and nothing more. Contrary to Applicants' assertions, the antisense oligonucleotides relied upon by Holst or Langin were used because of their ability to specifically hybridize with the target hsl nucleic acid and so are pertinent because they anticipate the antisense oligonucleotides claimed in the instant invention. Moreover, the primary sequence of hsl, its genetic organization and its biological relevance (e.g. its critical role in energy homeostasis as an enzyme that catalyzes the release of free fatty acids for transport as energy sources to energy requiring tissues) are taught by Holst and Langin, all of which are relevant and crucial for the motivation and means of targeting hsl for inhibition by antisense oligonucleotides.

Applicants also argue that the instant invention is not obvious over additional references of Mitchell and Milner because Mitchell provides no working examples of antisense that inhibit the target hsl and inhibit its activity, while Milner teaches a single oligonucleotide from an array of oligonucleotides tested that successfully targets and inhibits both alpha and beta globin synthesis. Contrary to Applicants' assertions, Mitchell teaches antisense oligonucleotides between 8-50 nucleobases in length that specifically target and inhibit the expression of hsl in vitro. This disclosure, combined with the teachings of Milner in disclosing the routine empirical screening of antisense for

their ability to inhibit the translation of any RNA target, render the instant invention obvious (e.g. see the abstract of Milner on page 537). Applicants assert that an extremely low demonstration of success for identifying antisense compounds that would inhibit target polynucleotides is demonstrated in the teachings of Milner and therefore these combination of references do not render the instant invention obvious. Contrary to applicants' assertions, the combinatorial technique taught by Milner allows for a simultaneous assessment of all possible oligonucleotides within a given region to inhibit target nucleic acid expression. The lack of correlation of predicted secondary mRNA structure with successful antisense inhibition was brought to light by the teachings of Milner, but this lack of correlation does not make the routine screening method for finding effective inhibitory antisense any less routine, it simply warns that one cannot design antisense based simply on secondary structural predications.

Applicants argue that the enablement rejection should be withdrawn because the instant disclosure teaches examples of in vivo targeting and inhibition of hsl. Applicants are correct that the instant disclosure is enabling for the in vivo targeting and inhibition of hsl expression in the liver of mice comprising the intraperitoneal administration of the antisense oligonucleotide of SEQ ID NO: 179. The 112, first paragraph rejections of record, however, address the enablement and written description requirements for the claims drawn to oligonucleotide mimetic compounds targeted to hsl and their ability to target and inhibit the expression of hsl in vitro and in vivo.

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